Exhibit A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application No. 10/526,697

Applicant: Mark E. DUDLEY et al.

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Examiner: Michail A. Belyavskyi

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Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building
401 Dulany Street
Alexandria, VA 22314

DECLARATION UNDER 37 CFR §1.132 OF MARK E. DUDLEY

Dear Sir:

I, Mark Dudley, hereby declare the following:

1. I am one of the named inventors of U.S. Patent Application No. 10/526,697 ("the instant application"). I am currently employed by the National Institutes of Health, the sole assignee of the instant application, as a Staff Scientist and Facility Head of the Tumor Immunology Section of the Surgery Branch. I received a Ph.D. in Biological Sciences from Stanford University in 1988. I worked as a Jane Coffin-Childs research fellow at the University of Pennsylvania and as a Cancer Research Institute/F. M. Kirby research fellow at the Jackson Laboratory prior to joining the Surgery Branch in 1996. I am also the first named author of Dudley et al., *J. Immunotherapy* 24: 363-373 (2001) (hereinafter, "Dudley 2001"); Dudley et al., *J. Clin. Oncol.*, published ahead of print on Sept. 22, 2008, available at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2008.16.5449 (hereinafter, "Dudley 2008;" copy attached); and Dudley et al. *Science* 298: 850-854 (published online Sept. 19, 2002) (hereinafter, "Dudley *Science* 2002;" copy attached).

2. It is my understanding that the current claim 23 reads as follows:

> A method of promoting the regression of a cancer in a mammal, which method comprises: (i) administering to the mammal nonmyeloablative lymphodepleting chemotherapy, and (ii) subsequently administering: (a) autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2, and, either concomitantly with the autologous T-cells or subsequently to the autologous T-cells, by the same or a different route, a T-cell growth factor that promotes the growth and activation of the autologous T-cells, or (b) autologous T-cells, which have been previously isolated, selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, and modified to express a T-cell growth factor that promotes the growth and activation of the autologous T-cells, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2, whereupon the regression of the cancer in the mammal is promoted.

3. Contrary to the expectations of one of ordinary skill in the art at the time the instant application was filed, administering nonmyeloablative lymphodepleting chemotherapy and subsequently administering autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer and which have undergone *one* cycle of rapid expansion provides unexpectedly superior clinical responses in patients as compared to methods in which patients were *not* administered nonmyeloablative lymphodepleting chemotherapy and in which the T-cells had undergone *multiple* cycles of rapid expansion.

4. Based upon my knowledge and experience, methods in which patients were not administered nonmyeloablative lymphodepleting chemotherapy and in which the T-cells had undergone multiple cycles of rapid expansion have produced poor objective clinical

responses, as measured by the Response Evaluation Criteria in Solid Tumors (RECIST)[1] or World Health Organization (WHO)[2] criteria (the two currently acceptable clinical standards).

5. For example, in Dudley 2001, 12 patients that had not been administered nonmyeloablative lymphodepleting chemotherapy were treated with 51 total infusions of cloned lymphocytes that underwent multiple cycles of rapid expansion (see, e.g., abstract, p. 365, right col. to p. 366, left col.). Zero patients had detectable transferred cells in the blood at two weeks (see, e.g., p. 370, right col.). Moreover, no patient in this study demonstrated an objective response of a greater than 50% reduction in all lesions and no new lesions, and all patients were considered nonresponders (see, e.g., p. 371, left col.).

6. Thus, one of ordinary skill in the art would recognize that this study resulted in zero objective responses as measured by the RECIST or WHO criteria.

7. Another study in which patients were not administered nonmyeloablative lymphodepleting chemotherapy and in which the T-cells had undergone multiple cycles of rapid expansion is described in Yee et al., *PNAS,* 99: 16168-73 (published online Nov. 11, 2002) (hereinafter, "Yee;" copy attached). In Yee, 10 patients that had not been administered nonmyeloablative lymphodepleting chemotherapy were treated with 43 total infusions of cloned lymphocytes that underwent multiple cycles of rapid expansion (see, e.g., abstract; page 16168, right col.). Zero patients had detectable transferred cells in the peripheral blood at three weeks (p. 16172, right col.). In addition, the treatment resulted in disease stabilization in 5 out of 10 patients and a minor or mixed response in 3 out of 10 patients (see, e.g., page 16171, right col.).

8. Thus, one of ordinary skill in the art would recognize that there were zero objective responses in the patients as measured by RECIST or WHO criteria.

9. Based on the results obtained in Dudley 2001 and Yee, one of ordinary skill in the art at the time the instant application was filed would not expect that T-cells that had

[1] RECIST criteria are described in Therasse et al., *J. Natl. Cancer Inst.* 92(3): 205-216 (2000) (copy attached).
[2] WHO criteria are described in Miller et al., *Cancer* 47: 207-214 (1981) (copy attached).

undergone only one cycle of rapid expansion would result in a positive, objective clinical response in patients.

10. Contrary to the expectations of one of ordinary skill in the art at the time the instant application was filed, methods in which patients were administered nonmyeloablative lymphodepleting chemotherapy and, subsequently, were administered T-cells which had undergone one cycle of rapid expansion have produced positive, objective clinical results as measured by RECIST criteria.

11. For example, in Example 1 of the instant application, thirteen patients received nonmyeloablative lymphodepeleting chemotherapy and, subsequently, were administered autologous T-cells which had been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2. Six of the 13 patients had objective clinical responses to treatment and four others demonstrated mixed responses with significant shrinkage of one or more metastatic deposits. Objective tumor regression was seen in the lung, liver, lymph nodes, and intraperitoneal masses, and at cutaneous and subcutaneous sites. Five patients, all with evidence of concomitant cancer regression, demonstrated signs of autoimmune melanocyte destruction. These results were published in Dudley *Science* 2002.

12. The study described in Example 1 of the instant application was expanded as described in Dudley 2008. In Dudley 2008, 43[3] patients were administered nonmyeloablative lymphodepleting chemotherapy and, subsequently, received 46 total infusions of autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2 (see, e.g., p. 2). In contrast to the

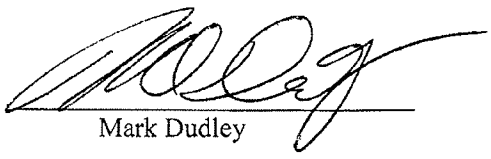
[3] The 43 patients in the study of Dudley 2008 includes the thirteen patients of Example 1 of the instant application which are referred to in ¶ 11.

results obtained in Dudley 2001 and Yee, the Dudley 2008 method resulted in objective, clinical responses measured by RECIST criteria in 21 out of the 43 patients (48%) (see, e.g., Table 2). Tumor regression was seen in metastases at virtually all visceral and soft tissue sites including brain. In addition, a majority of patients had detectable levels of transferred cells in circulation at one month after treatment (data not shown in paper).

13. Thus, contrary to the expectations of one of ordinary skill in the art at the time the instant application was filed, a method in which patients are administered nonmyeloablative lymphodepleting chemotherapy and, subsequently, are administered T-cells which have undergone one cycle of rapid expansion have unexpectedly produced positive, objective clinical results, as shown, for example, in Dudley 2008.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issued thereon.

10-1-08
Date


Mark Dudley